



Air Particle Pollution Pollutant Exposure **Translocation** Uptake into Deposition in Pulmonary Nose & Lung Tissue Endocytotic pathways & Olfactory Bulb Airways and Alveoli Interaction Macrophage associated Molecular Initiating Event Epithelium - Chemokines Direct -Oxidative Cellular **CNS** Macrophages - Pro-inflammatory Cytokines stress Response **Effects** Receptor Activation Autonomic Systemic Oxidative Circulatory Systemic Nervous System Stress & Inflammation System Effects Intermediate Fat Liver Sites of Action Adipokines PAI-1 Acute phase response Insulin resistance, Endothelial Endothelial dysfunction Endothelial Biochemical dysfunction Vasoconstriction, Platelet Aggregation dysfunction Lipoprotein modification & Physiological Vasoconstriction Platelet Aggregation Pro-thrombotic effects. Responses Neural-mediated ROS Vasoconstriction Anti-fibrinolytic effects Sub-Clinical & Increased Atherosclerosis progression/plaque Increased HR Clinical Responses BP vulnerability, Thrombosis & BP Myocardial Clinical Arrhythmia Stroke DVT/PF Heart Failure Infarction Events

ED_001449_00000015

Proposed Adverse Outcome Pathways Explaining Ambient Air Particle Pollution Exposure and Premature Death from Arrhythmia

Short-term
Triggers of
Arrhythmia
&
Long-term
Drivers of
Cardiac
Remodeling

Cardiac

Structural

&

Electrical

Remodeling

RAS Endothelin Cymorphisms

Unflammatory mediators

ANS Imbalance

Air Particle Pollution

Hypertension Diabetes Age

Myocardial Ischemia

Membrane Active Chemicals

Channelopathies

Modifiers of Cardiac Electrophysiology

Active & Passive Cardiac Membrane Properties

Fiber direction
Hypertrophy
Extracellular matrix
Focal fibrosis/Scar
LV dilation/stretch



Altered –
Ionic homeostasis
Intercellular
communication
Calcium handling

Biomarkers & Clinical Outcomes

Clinical Events

Ventricular Arrhythmia Sudden death



Electrocardiographic Markers

Repolarization changes (QTc and Te-Tp prolongation; T-wave complexity, T-wave alternans; repolarization reserve)

ED_001449_00000015